Remarks

Claims 4-6, 10-12, and 17-19 are pending and rejected. Claims 1-3, 7-9, and 13-16 have been cancelled.

Rejections under 35 U.S.C. 112

Claims 4-6 and 17-19 have been rejected as not enabled as required by 35 U.S.C. § 112, first paragraph, for use of the phrase "an effective amount". Claims 4-6 and 17 have been rejected as indefinite under 35 U.S.C. § 112, second paragraph. These rejections are respectfully traversed.

Enablement

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003; *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Claims 4-6 and 17-19 are enabled

A proper analysis of the *Wands* factors shows that claims 4-6 and 17-19 satisfy the enablement requirement. Applicants do not understand how the Examiner can allege that the claims are obvious, and then suggest that they are not enabled! The quantity of experimentation necessary to obtain and use the claimed angiogenesis inhibitors for the treatment of the recited disorders is **not undue.**

The angiogenesis inhibitors that may be used in the claimed methods are disclosed in the specification on page 6, line 4 to page 7, line 10 along with a number of references which thoroughly describe these agents and **effective amounts for use in humans, and methods of administration.** In addition, the specification also teaches how to make pharmaceutical compositions of the compounds and methods that can be used to administer the drugs to patients

(see, for example, pages 12-14). Furthermore, the specification lists the diseases that may be treated on page 5, line 15 to page 6, line 2. These diseases are also well-known and characterized and can be found in any medical textbook.

The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). There is no requirement for examples nor is there any need for examples in this application. The claimed agents are known (although **not** for the treatment of the recited disorders), well-characterized and commercially available. Therefore, one of ordinary skill in the art could routinely arrive at an effective amount of the drugs and method of delivery to treat the claimed disorders. Furthermore, as discussed below, the term "effective amount" is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation, as is the case here.

Additional evidence that one can determine an effective amount of drug, even one of much less than ordinary skill in the art such as the undersigned, is provided in the accompanying abstracts of the papers by LoTempio, et al., Clin. Cancer Res. 1:11(19 Pt 1):6994-7002 (2005) (curcumin topical paste) and Li, et al., Cancer 104(6):1322-1331 (2005) (liposomally encapsulated curcumin).

In summary, it is clear from the guidance in the specification, the state of the prior art, and the level of skill in the art that one of ordinary skill in the art would be able to use the claimed angiogenesis inhibitors to treat the recited disorders without undue experimentation.

Definiteness

The Legal Standard

According to 37 CFR 1.75 (c), "One or more claims may be presented in dependent form, referring back to and further limiting another claim or claims in the same application. [...] Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim." Thus if a claim depends from another claim, the dependent claim includes all the limitations of the claim from which it depends, without restating those limitations.

The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). The fact that other language may be used in a claim is not a valid basis for a rejection under 35 U.S.C. § 112, second paragraph. The M.P.E.P. explains that the examiner's focus during examination of claims for compliance with the definiteness requirement "is whether the claim meets the threshold requirements of clarity and precision, *not whether more suitable language or modes of expression are available*." (M.P.E.P. 2173.02, emphasis added) The M.P.E.P. further explains that "[s]ome latitude in the manner of expression and the

aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire." (*Id.*)

The rejection of the claims over the term "effective amount" is legally improper. This term is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation. (See, e.g., *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003); *In re Halleck*, 57 C.C.P.A. 954, 422 F.2d 911, 914 (CCPA 1970). An effective amount of the angiogenesis inhibitor is an amount as required to alleviate the symptoms of the particular disorder being treated (page 14, lines 28-29). Since the claimed angiogenesis inhibitors are known and characterized compounds (although not for the treatment of the recited disorders), one of ordinary skill in the art could arrive at an "effective amount" of any one of these drugs to treat the listed disorders.

Rejections over the Prior Art

Claim 17 was rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,218,368 to Wirostko ("Wirostko"). Claims 4 and 5 were rejected under 35 U.S.C. § 103 (a) as being obvious over U.S. Patent No. 5,190,918 to Deutch, et al., in view of U.S. Patent No. 6,482,801 to Brem, et al. or Deutch, et al., in view of U.S. Patent No. 5,654,312 to Andrulis, Jr. Claims 4-6 were rejected under 35 U.S.C. 103 as obvoius over Deutch in view of U.S. Patent No. 5,776,898 to Teicher, et al. Claims 10-12 and 18 have been rejected as obvious over WO 95/18606 to Aggarwal. Claims 10-12 and 19 were also rejected as obvious under 35 U.S.C. 103

over Arbiser, et al. J. Amer. Acad. Dermatol. 40, No. 6, 925-929 (June 1999) in view of Thaloor, et al. Cell Growth & Differentiation 9, 305-312 (April 1998) and Aggarwal.

Rejection Under 35 U.S.C. § 102

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-

maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention.").

Wirostko

Wirostko describes systemic administration of a tetracycline to treat acne rosacea. Wirostko is administering a tetracycline for its common antibiotic activity and is using the common misnomer of acne rosacea to refer to acne characterized by redness. Acne is actually an infection of the skin; rosacea is a different disease. Attached is a printout from the National Rosacea Society that explains the criteria, causes, and differences with acne (and confusion in nomenclature).

Rejections Under 35 U.S.C. § 103

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177

(C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier* , 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the describeing or motivation to combine prior art references."

In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit describeings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed.

Deuth

Deuth, et al. allegedly shows that angiogenesis activity is the ability to enhance the formation of lymph vessels. This is completely contrary to any common definition of angiogenesis, which is defined in the application at page 2 and in the literature as relating to the initiation and growth of blood vessels.

Deuth in combination with Brem

Brem, et al. acknowledges that minocycline is an angiogenesis inhibitor and a collagenase inhibitor.

There is nothing that would lead one skilled in the art of treating lymphangiogenesis to adopt the peculiar description of Deuth and combine it with Brem, et al., with any expectation of success. Attached is an article, Jussila and Alitalo, "Vascular Growth Factors and

Lymphangiogenesis" Physiol. Rev. 82, 673-700 (2002) that explains and differentiates angiogenesis and lymphangiogenesis. While not prior art, it establishes the important differences between angiogenesis and lymphanigiogenesis. While both are extremely important, they are not the same, and a reference to one would not lead one to assume the same with respect to the other.

Deuth in combination with Andrulis

Deuth, et al. is discussed above. Andrulis does not lead one to extrapolate from lymphangiogenesis to angiogenesis nor that there would be any expectation that thalidomide, referenced by Andrulis with respect to inhibiting angiogenesis, would be effective in preventing lymphangiogenesis.

Deuth in combination with Teicher

Deuth is discussed above. Teicher is no different than Andrulis or Brem. It also discloses only a compound known to inhibit angiogenesis, TNP-470, not lymphangiogenesis. There is nothing to lead one of ordinary skill in the art to extrapolate from angiogenesis to lymphagiogenesis; no reference that would motivate one skilled in the art to have a reasonable expectation of success in using a compound known to inhibit angiogenesis to inhibit lymphangiogenesis.

Aggarwal

Aggarwal has been cited as making obvious claims 10-12 and 18. Claim 10 defines a method to treat the symptoms associated with elevated basic fibroblast growth factor in a disorder selected from the group consisting of angiosarcoma, hemangioendothelioma, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Kaposi's sarcoma, psoriasis, and

recessive dystrophic epidermolysis bullosa, comprising administering to the individual in need of treatment an effective amount of a pharmaceutical composition comprising a curcuminoid in combination with a pharmaceutically acceptable carrier to inhibit angiogenesis, wherein the carrier is an ointment for topical administration containing between one-half percent (0.5%) and five percent (5%) of the curcuminoid or a polymer formulation for implantation.

It is difficult to understand how the use of this formulation could be obvious, since the same examiner previously allowed claims to the composition *per se*, in the now issued parent application, U.S. Patent No. 6,673,843.

Indeed, the composition is not obvious, nor is the use in any of the defined conditions obvious. The examiner has cited no evidence why one skilled in the art would have any motivation to treat completely different disorders with the claimed formulation, nor why one would have any expectation of success based on a reference using a hugely different amount of drug (1 microgram to 100 milligrams) as compared to the amount in the claimed formulation. It is not enough to make allegations that a reference makes something obvious; the rejection must be based on a factual analysis that one skilled in the art would be led to the difference defined by the claims, and have a reasonable expectation of success.

Arbiser in view of Thaloor and Aggarwal

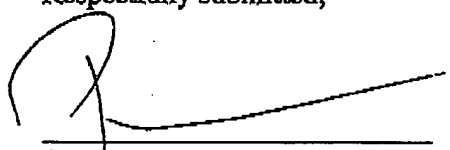
Arbiser is not prior art to this application. This application claims priority to June 30, 1999. Arbiser is published in June 1999. To the extent it might be prior art to this application under 35 U.S.C. 102(a), it is clear that it could be removed as prior art as the inventor's own

publication (note that it is Dr. Arbiser to whom inquiries are to be directed). However, as the examiner has noted, this paper does not describe administering curcumin.

Thaloor does not make up for this deficiency. Arbiser says there are at least two mechanisms – the role of basic fibroblast growth factor and angiogenesis involved in recessive dystrophic epidermolysis bullosa. Nothing the examiner cites lead one to expect curcumin to treat both mechanisms, therefore there would be no expectation of success. One would instead believe that TNP-470, which is administered systemically, not curcumin, administered as an ointment, would be effective. Aggarwal, discussed above, does not make up for this deficiency.

In summary, the claims are definite, novel and not obvious over the prior art.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 21,284

Date: October 28, 2005

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)